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JONES DAY 222 EAST 41ST ST NEW YORK, NY 10017			BOESEN, CHRISTIAN C	
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/551,300	<b>Applicant(s)</b> TROTTA, CHRISTOPHER R.	
	<b>Examiner</b> CHRISTIAN BOESEN	<b>Art Unit</b> 1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 19 August 2009.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 26-48 is/are pending in the application.
- 4a) Of the above claim(s) 29-39, 47 and 48 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 26-28 and 40-46 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>08/19/2009</u> . | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

This Final Office Action is responsive to the communication received 08/19/2009.

#### ***Claim Status***

Claim(s) 26 has been amended as filed on 08/19/2009.

Claim(s) 26-48 are currently pending.

Claim(s) 29-39 and 47-48 have been withdrawn.

Claim(s) 26-28 and 40-46 are being examined in this application.

#### ***Election/Restrictions***

Applicant's election without traverse in the reply filed 11/10/2008 of group I, claims 26-48 is noted. Applicant election in the reply filed 11/10/2008 of the species A. measuring the ligation of half molecules; B. animalia tRNA splicing ligase; C. human cell-free extract; D. isoprenoid library is noted.

#### ***Priority***

This application for patent is filed under 35 U.S.C 371 of PCT/US04/09590 (filed on 03/26/2004).

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Acknowledgment is made for priority to a provisional application 60/458,067 03/27/2003.

***Information Disclosure Statement***

The information disclosure statement filed 08/19/2009 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein regarding the crossed out references (see the attached PTO-1449) has not been considered.

**Claim Objection(s) / Rejection(s) Maintained**

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

**Claims 26-28, 40-42, and 45-46** are rejected under 35 U.S.C. 103(a) as being unpatentable over Greer (Molecular and Cellular Biology, 1986, volume 6 page 635) in combination with Rana (WO 01/25486 A1) and Li (Science, 1998, volume 280 page 279).

Claims are drawn to a method of identifying a compound that modulates the activity of an animalia or human tRNA splicing ligase. This method comprises first contacting a population of 5' tRNA half molecules and a population of 3' tRNA half molecules with tRNA splicing ligase and a compound or a member of a library of compounds, measuring the ligation of the half molecules, identification of compounds that inhibit or enhance tRNA splicing ligase activity, and determining the structure of the identified compound.

**Greer teaches** a method of contacting a population of 5' tRNA half molecules and a population of 3' tRNA half molecules with **yeast** tRNA splicing ligase and measuring the ligation of the half molecules (page 636, bottom right, "Preparation of pre-tRNA substrates. Unlabeled tRNA precursors were purified..."; page 636, bottom right, "Preparation of tRNA halves. Paired tRNA halves were prepared by preincubating endonuclease..."; page 637, top left, "Measurement of endonuclease and ligase activities. Titrations of endonuclease and ligase activity were carried out in reactions ... of unlabeled pre-tRNA plus... <sup>32</sup>P-labeled SUP6 transcript.... Samples were then analyzed by electrophoresis.... Reaction products were quantitated by measuring Cerenkov radiation in gel slices.")

Greer does not teach **identification of compounds** that inhibit or enhance tRNA splicing ligase.

**Rana teaches** identification of compounds that bind RNA (page 3, line 28, "In a first embodiment, the present invention relates to a method for identifying a test compound that binds

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to a target RNA molecule, comprising the steps of: (a) contacting a dye-labeled target RNA molecule with substantially one type of test compound attached to a solid support, thereby providing a dye-labeled target RNA:support-attached test compound complex; and (b) determining the structure of the substantially one type of test compound of the RNA:test compound complex." and page 3, line 35, "In a second embodiment, the present invention relates to a method for identifying a test compound that binds to a target RNA molecule, comprising the step of determining the structure of substantially one type of test compound of an RNA:test compound complex formed from contacting a dye-labeled target RNA molecule with substantially one type of test compound attached to a solid support.").

**Rana teaches** that identified RNA binding compounds can inhibit or enhance the activity of RNA binding enzymes (abstract, "The present invention further relates to methods of inhibiting an RNA-protein interaction, to methods of screening for compounds that increase or decrease the production of a protein" and page 8, line 14, " Compounds that bind to mRNA can, *inter alia*. increase or decrease the rate of mRNA processing, alter its transport through the cell, prevent or enhance binding of the mRNA to ribosomes, suppressor proteins or enhancer proteins, or alter mRNA stability. Accordingly, compounds that increase or decrease mRNA translation can be used to treat or prevent disease.")

**Rana teaches** identifying RNA binding compounds including (page 16, line 22, "Types of test compounds include, but are not limited to, peptides, peptide analogs including peptides comprising non-natural amino acids, *e.g.*, D-amino acids (see Table 1, below), phosphorous analogs of amino acids, such as  $\alpha$ -amino phosphonic acids and  $\alpha$ -amino phosphinic acids, or amino acids having non-peptide linkages, nucleic acids, nucleic acid analogs such as

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phosphorothioates or peptide nucleic acids ("PNAs"), hormones, antigens, synthetic or naturally occurring drugs, opiates, dopamine, serotonin, catecholamines, thrombin, acetylcholine, prostaglandins, organic molecules, pheromones, adenosine, sucrose, glucose, lactose and galactose.")

**Rana teaches** a library of compounds (page 19, line 31, "Combinatorial compound libraries useful for the methods of the present invention...")

**Rana teaches** determining the structure of the identified compound (page 22, line 6, "A variety of direct techniques for determining the structure of test compounds on solid supports are useful in the methods of the invention. In embodiments where the test compound is a peptide or oligonucleotide, the structure of these compounds can be determined by standard peptide or oligonucleotide sequencing techniques, respectively. In some embodiments, the library will not comprise test compounds wherein structures can be determined by sequencing techniques, since the test compounds are not limited to peptides or nucleic acids. In some embodiments, structures of test compounds are determined using NMR techniques, such as high resolution magic angle spinning NMR spectroscopy (Warrass et al. (1999) J. Am. Chem. Soc. 121:3787-3788). In these embodiments, the test compounds are not cleaved from the solid support, thus eliminating an extra chemistry step that may destroy them. Instead, NMR spectra of support-bound test compounds are collected and sophisticated solvent suppression techniques are applied based on differential diffusion behavior of solvent and compounds attached to the solid supports, which allow for greater signal-to-noise ratios and resolution in the spectra.

In other embodiments, Fourier transform infra-red spectroscopy (FTIR) or Fourier transform Raman spectroscopy (FT-Raman) can be used to decode a solid support by determining structure of the test compound bound thereto (Yan et al. (1999) J. Comb. Chem. 1:46-54). The advantage of these techniques is that they are sensitive to changes in organic functional groups and can be performed on a single solid support. In still other embodiments, electrospray ionization (ESI) mass spectrometry or matrix-assisted laser desorption/ionization (MALDI) mass spectrometry, either alone or coupled with HPLC or other separation techniques, are used in the methods of the invention (Submuth et al. (1999) J. of Chromatography B 725:49-65). The mass spectrometry methods are sensitive methods requiring only small amounts of sample that can be the test compounds either after cleavage or while on the solid support. In yet other embodiments, X-ray photoelectron spectroscopy is used to identify the structure of test compounds (Yoo et al. (1999) J. Comb. Chem. 1(3): 177-180). This technique utilizes a resin modified with a suitable heteroatom, such as bromine, which interacts with heteroatoms in the test compound being synthesized in order to monitor, *e.g.*, coupling efficiencies and reaction times, or to identify products of a synthesis.

Indirect techniques for determining the structure of a test compound on a solid support involve decoding one or more readable tags on the solid support that do not include the test compound itself, but that have about a one-to-one correspondence with a particular test

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compound, such that identification of one or more tags associated with a solid support unequivocally identifies the structure of the test compound.

In a preferred embodiment, test compounds are synthesized on a solid support, and during each step of the synthesis, readable molecular tags that encode the step number and the chemical reagent used in that step are attached to the support (Ohlmeyer et al. (1993) Proc. Natl. Acad. Sci. USA 90: 10,922-10,926; Still (1996) Acc. Chem. Res. 29: 155-163). In this embodiment, the readable tags provide a history of the synthesis as well as identify the test compound on the support. The tags are cleaved from the solid support and read by, *e.g.*, electron capture gas chromatography, in order to decode the support. Different types of readable molecular tags useful in embodiments of the present invention that employ readable molecular tags to decode solid supports will be apparent to those skilled in the art and include oligonucleotides, peptides and small organic molecules (see Nefzi et al. (1997) Chem. Rev. 97:449-472; Lam et al. (1997) Chem. Rev. 97:411-448).

In other embodiments, decoding a solid support involves the use of laser optical synthesis chips (LOSCS) (Xiao et al. (1997) Angew. Chem. Int. Ed. Engl. 36(7):780-782). This technology does not involve the use of chemical tags, but rather bar codes etched into the solid support with a laser. If each bar code is associated with a particular test compound, reading the bar code on the solid support will identify the structure of the test compound attached to the solid support. In still other embodiments, fluorescently labeled solid supports can be used for the synthesis of a library of test compounds, and the fluorescence spectra of the fluorescent labels can be used to identify the structure of the test compounds thereon (Yan et al. (1998) J. Comb. Chem. 1 (1):78-81)."

It would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to use Rana's method for identifying RNA binding compounds in Greer's method of contacting a population of 5' tRNA half molecules and a population of 3' tRNA half molecules with tRNA splicing ligase and measuring the ligation of the half molecules **to arrive at applicant's invention with the above cited references before them.**

One would have been motivated to identify RNA binding compounds in an assay by screening with a library of compounds followed by determining the structure of the identified compound in Greer's method because Rana teaches that RNA binding compounds can modulate protein expression and these compounds could be used in treating a disease such as HIV infection (page 4, line 10,



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"In a fourth embodiment, the present invention relates to a method for increasing or decreasing the production of a protein comprising the step of contacting a target messenger RNA molecule that encodes said protein with the test compound identified from a method comprising the steps of: (a) contacting a dye-labeled target RNA molecule with substantially one type of test compound attached to a solid support, thereby providing a dye-labeled target RNA:support-attached test compound complex; and (b) determining the structure of the substantially one type of test compound of the RNA:test compound complex.

In a fifth embodiment, the present invention relates to a method for treating or preventing a disease whose progression is associated with *in vivo* binding of a test compound to a target RNA, comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of the test compound, or a pharmaceutically acceptable salt thereof, identified according to a method comprising the steps of: (a) contacting a dye-labeled target RNA molecule with substantially one type of test compound attached to a solid support, thereby providing a dye-labeled target RNA:support-attached test compound complex; and (b) determining the structure of the substantially one type of test compound of the RNA:test compound complex.

In a sixth embodiment, the present invention relates to a method for treating or preventing HIV infection or AIDS in a patient, comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound ...").

and because Rana teaches that the advantage of using libraries is that numerous compounds can be screened in an assay, and then the structure of the identified compound can be determined (page 6, line 12, "Thus, the methods of the present invention provide a simple, sensitive assay for highthroughput screening of entire test compound libraries, where test compounds in a library that bind an RNA of interest are easily separated from non-RNA-binding compounds, and where the structures RNA-binding and, accordingly, active test compounds are easily determined by encoding methods.")

One would have had a reasonable expectation of success to identify RNA binding compounds that modulate tRNA splicing ligase using a library of compounds and a tRNA ligation assay because screening for RNA binding compounds using of libraries is well established in the art as evidenced by Rana (page 6, line 1, The present invention relates to a

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method for identifying a test compound that binds to RNA using a library of test compounds attached to a solid support.")

Thus, the present invention would have been *prima facie* obvious at the time the invention was made.

Greer does not teach **animalia or mammalian or human** tRNA splicing ligase.

**Li teaches** that all Eucarya tRNA splicing ligases are related (page 279 top left, "Introns are found in the tRNA genes of organisms in all three of the great lines of descent: the Eucarya, the Archaea, and the Bacteria. In Bacteria, tRNA introns are self-splicing group I introns and the splicing mechanism is autocatalytic (1). In Eucarya, tRNA introns are small and invariably interrupt the anticodon loop 1 base 39 to the anticodon. They are removed by the stepwise action of an endonuclease, a ligase, and a phosphotransferase (2). In Archaea, the introns are also small and often reside in the same location as eucaryal tRNA introns (3). Splicing in Archaea is catalyzed by an endonuclease, but the mechanism of ligation is likely different from that in Eucarya as there is no homolog of the eucaryal tRNA splicing ligase in the complete genome sequence of several members of the Archaea (4)."

The present claims would have been obvious because the **substitution** of one known element, animalia (including mammalian including human) tRNA splicing ligase (genus Eucarya), taught by Li for another, yeast tRNA splicing ligase (genus Eucarya), taught by Greer would have yielded predictable results to one of ordinary skill in the art at the time of the invention (i.e. modulating human tRNA splicing ligase activity). See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007).

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All the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Thus the present invention would have been *prima facie* obvious at the time the invention was made.

*Discussion and Answer to Argument*

Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of Applicant's traversal is addressed below (Applicant's arguments are in italic):

1.      *Applicant asserts "Greer does not teach or suggest screening assays to identify compounds that modulate the activity of yeast tRNA ligase, much less screening assays to identify compounds that modulate the activity of animalia tRNA ligase. In fact, there is no teaching or suggestion to use animalia tRNA ligase at all in Greer. Moreover, Greer does not provide any motivation to one of ordinary skill in the art to screen for compounds that modulate the activity of animalia tRNA ligase." (Reply page 7 bottom).*

In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Further, Applicants are also respectfully directed to the Supreme Court decision, which forecloses the argument that a specific teaching, suggestion, or motivation is required in the references to support a finding of obviousness. *KSR*, 127 S.Ct. at 1741, 82 USPQ2d at 1396.

2. *Applicant asserts "Rana does not teach or suggest screening for compounds that modulate the activity of an enzyme, much less an animalia tRNA ligase. In fact, Rana does not even mention tRNA splicing ligase, much less provide any assays for evaluating whether a compound can modulate the activity of a tRNA splicing ligase. Moreover, the description in Rana relating to modulating protein production and treating or preventing diseases relates to mRNA not precursor tRNA or pre-tRNA half-molecules, which are substrates for eukaryotic tRNA splicing ligase. Thus, contrary to the Examiner's allegation, one of ordinary skill in the art would not have been motivated to modify the methods of Rana for identifying compounds that bind to a target RNA molecule to develop a method for identifying compounds that modulate the activity of an animalia tRNA splicing ligase, even in view of Greer which relates to understanding the splicing of tRNA precursors in S. cerevisiae." (Reply page 8 center).*

In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Further, Applicants are also respectfully directed to the Supreme Court decision, which forecloses the argument that a specific teaching, suggestion, or motivation is required in the references to support a finding of obviousness. *KSR*, 127 S.Ct. at 1741, 82 USPQ2d at 1396.

Applicants also argue there is no motivation to combine the cited references. It would be obvious to **combine** Greer's method of contacting a population of 5' tRNA half molecules and a population of 3' tRNA half molecules with tRNA splicing ligase and measuring the ligation of the half molecules with Rana's method for identifying RNA binding compounds because Rana teaches that RNA binding compounds can modulate protein expression and these compounds could be used in treating a disease such as HIV infection. In addition, Rana also teaches that the advantage of using libraries is that numerous compounds can be screened in an assay, and then the structure of the identified compound can be determined. In addition, it would be useful to identify compounds that bind to a target RNA molecule because such compounds could block or modulate the activity of tRNA splicing ligase. Such compounds could be nonspecific or specific. Nonspecific tRNA splicing ligase inhibition compounds could be useful in the localized administration to kill cells, such as a tumor. Specific compounds could be useful to regulate the expression of specific tRNAs that generated by tRNA splicing ligase.

3. *Applicant asserts "there is no teaching or suggestion in Li that yeast tRNA splicing ligase can be substituted with the animalia tRNA ligase." (Reply page 9 top).*

In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

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Further, Applicants are also respectfully directed to the Supreme Court decision, which forecloses the argument that a specific teaching, suggestion, or motivation is required in the references to support a finding of obviousness. *KSR*, 127 S.Ct. at 1741, 82 USPQ2d at 1396.

Applicants also argue there is no motivation to combine the cited references. It would be obvious to **substitute** of one known element, animalia (including mammalian including human) tRNA splicing ligase (genus Eucarya), taught by Li for another, yeast tRNA splicing ligase (genus Eucarya), taught by Greer because Li teaches that all Eucarya tRNA splicing ligases are related. Thus, proteins with a similar structure and function can be substituted. Rana teaches a reason to substitute human for yeast is to identifying RNA binding compounds that can modulate protein expression and these compounds could be used in treating a disease such as HIV infection (a human disease).

**Claims 42 and 43-44** are rejected under 35 U.S.C. 103(a) as being unpatentable over Greer (Molecular and Cellular Biology, 1986, volume 6 page 635) in combination with Rana (WO 01/25486 A1) and Li (Science, 1998, volume 280 page 279) **above** and in further view of Kaminska (FEMS Yeast Research, 2002, volume 2 page 31).

Claims are drawn to a method of identifying a compound that modulates the activity of an animalia or human tRNA splicing ligase. This method comprises first contacting a population of 5' tRNA half molecules and a population of 3' tRNA half molecules with tRNA splicing ligase and a compound or a member of a library of **isoprenoid** compounds.

Greer, Rana, and Li teach the claimed methods as discussed above.

Neither Greer nor Rana nor Li teach isoprenoid compounds.

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Kaminska teaches that tRNA levels alter the isoprenoid biosynthetic pathway (abstract "tRNA isopentenylolation is a branch of an isoprenoid pathway in yeast. There is a competition for a substrate between isoprenoid biosynthetic enzyme Erg20p and tRNA isopentenyltransferase." and page 32, left center, "It was shown recently that the levels of tRNA are elevated in *maf1-1* cells and that Maf1p acts as a negative regulator of tRNA transcription [20]." and page 34, left center, "In *maf1-1*, the level of Erg20p was elevated 1.69-fold as compared to the isogenic wt strain (Fig. 2)."

It would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to use isoprenoid compounds in Rana's method of identifying RNA binding compounds in an assay starting with a compound or a library of compounds **to arrive at applicant's invention with the above cited references before them.**

One would have been motivated to use a library of isoprenoid compounds in Rana's method of identifying RNA binding compounds because Kaminska teaches that tRNA levels alter the isoprenoid biosynthetic pathway (abstract "tRNA isopentenylolation is a branch of an isoprenoid pathway in yeast. There is a competition for a substrate between isoprenoid biosynthetic enzyme Erg20p and tRNA isopentenyltransferase." and page 32, left center, "It was shown recently that the levels of tRNA are elevated in *maf1-1* cells and that Maf1p acts as a negative regulator of tRNA transcription [20]." and page 34, left center, "In *maf1-1*, the level of Erg20p was elevated 1.69-fold as compared to the isogenic wt strain (Fig. 2)."

One would have had a reasonable expectation of success to identify RNA binding compounds using an isoprenoid library because screening for RNA binding compounds using various different types of libraries are well established in the art as evidenced by Rana (page 16,

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bottom, "Types of test compounds include, but are not limited to, peptides, peptide analogs including peptides comprising non-natural amino acids, *e.g.*, D-amino acids (see Table 1, below), phosphorous analogs of amino acids, such as  $\alpha$ -amino phosphonic acids and  $\alpha$ -amino phosphinic acids, or amino acids having non-peptide linkages, nucleic acids, nucleic acid analogs such as phosphorothioates or peptide nucleic acids ("PNAs"), hormones, antigens, synthetic or naturally occurring drugs, opiates, dopamine, serotonin, catecholamines, thrombin, acetylcholine, prostaglandins, organic molecules, pheromones, adenosine, sucrose, glucose, lactose and galactose." and page 19, line 31, "Combinatorial compound libraries useful for the methods of the present invention...").

Thus, the present invention would have been *prima facie* obvious at the time the invention was made.

#### Discussion and Answer to Argument

Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of Applicant's traversal is addressed below (Applicant's arguments are in *italic*):

1. *Applicant asserts "Kaminska does not teach or suggest tRNA splicing. There is no teaching or suggestion in Kaminska regarding tRNA splicing ligase or the use of such a ligase in a method for screening for compounds that modulate tRNA splicing ligase, much less an animalia tRNA splicing ligase or the use of an animalia tRNA splicing ligase in such a screening*



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*method. Moreover, there is no teaching or suggestion in Kaminska that an isoprenoid compound would have any effect on tRNA splicing, much less an animalia tRNA splicing ligase.*

*Based on the teachings of Kaminska, taken alone or in combination with Greer and Li, it is unclear how the relationship between tRNA levels and tRNA isopentenylolation and the isoprenoid pathway would suggest that using an isoprenoid compound would have any effect on the activity of an animalia tRNA splicing ligase. In particular, it is unclear how the teaching in Kaminska of the competition between tRNA isopentenyltransferase and an enzyme in the isoprenoid biosynthetic pathway for the substrate DMAPP would have suggested screening for an isoprenoid compound that modulated tRNA splicing. Accordingly, Kaminska would not have provided one of ordinary skill in the art with a motivation to screen for an isoprenoid compound that modulates the activity of an animalia tRNA splicing ligase." (Reply page 9 top).*

In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Further, Applicants are also respectfully directed to the Supreme Court decision, which forecloses the argument that a specific teaching, suggestion, or motivation is required in the references to support a finding of obviousness. *KSR*, 127 S.Ct. at 1741, 82 USPQ2d at 1396.

Applicants also argue there is no motivation to combine the cited references. It would be obvious to **substitute** Rana's library of compounds with a library of isoprenoid compounds when using Greer's method of contacting a population of 5' tRNA half molecules and a population of 3' tRNA half molecules with tRNA splicing ligase and measuring the ligation of the half molecules

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because Kaminska teaches that tRNA levels alter the isoprenoid biosynthetic pathway.

Biosynthetic pathways can involve positive and negative feedback loops. As such, isoprenoid compounds may modulate tRNA splicing activity.

### *Summary*

The 103 rejection is based in the obviousness of combining multiple references and not the references individually. It would be obvious to **combine** Greer's method of contacting a population of 5' tRNA half molecules and a population of 3' tRNA half molecules with tRNA splicing ligase and measuring the ligation of the half molecules with Rana's method for identifying RNA binding compounds because Rana teaches that RNA binding compounds can modulate protein expression and these compounds could be used in treating a disease such as HIV infection. In addition, Rana also teaches that the advantage of using libraries is that numerous compounds can be screened in an assay, and then the structure of the identified compound can be determined. In addition, it would be useful to identify compounds that bind to a target RNA molecule because such compounds could block or modulate the activity of tRNA splicing ligase. Such compounds could be nonspecific or specific. Nonspecific tRNA splicing ligase inhibition compounds could be useful in the localized administration to kill cells, such as a tumor. Specific compounds could be useful to regulate the expression of specific tRNAs that generated by tRNA splicing ligase. It would be obvious to **substitute** of one known element, animalia (including mammalian including human) tRNA splicing ligase (genus Eucarya), taught by Li for another, yeast tRNA splicing ligase (genus Eucarya), taught by Greer because Li teaches that all Eucarya tRNA splicing ligases are related. Thus, proteins with a similar structure

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and function can be substituted. Rana teaches a reason to substitute human for yeast is to identifying RNA binding compounds that can modulate protein expression and these compounds could be used in treating a disease such as HIV infection (a human disease). It would be obvious to **substitute** Rana's library of compounds with a library of isoprenoid compounds when using Greer's method of contacting a population of 5' tRNA half molecules and a population of 3' tRNA half molecules with tRNA splicing ligase and measuring the ligation of the half molecules because Kaminska teaches that tRNA levels alter the isoprenoid biosynthetic pathway. Biosynthetic pathways can involve positive and negative feedback loops. As such, isoprenoid compounds may modulate tRNA splicing activity.

### ***Conclusion***

No claim is allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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Any inquiry concerning this communication or earlier communications from the Examiner should be directed to CHRISTIAN BOESEN whose telephone number is 571-270-1321. The Examiner can normally be reached on Monday-Friday 9:00 AM to 5:00 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christopher S. Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christian Boesen/  
Examiner, Art Unit 1639

/SUE LIU/  
Primary Examiner, Art Unit 1639